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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 08/791,240 | 01/30/97 | RYNCARZ A | BDI-1020 |

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| EXAMINER | |
|---|---|
| SISSON, B | |
| **ART UNIT** | **PAPER NUMBER** |
| 1655 | 42 |

**DATE MAILED:** 10/05/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/791,240 | RYNCARZ, ALEXANDER J. | |
| | Examiner | Art Unit | |
| | Bradley L Sisson | 1655 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 July 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-57 and 59-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-57 and 59-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 1997* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-52 and 59-65 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

*The Quantity of Experimentation Necessary*

The quantity of experimentation needed to practice the full scope of the claimed invention is great, on the order of several man years with little, if any, reasonable expectation of success.

*The Amount of Direction or Guidance Provided*

The amount of guidance provided is limited.

*The Presence or Absence of Working Examples*

The specification presents but one example, found at pages 74-77.

*The Nature of the Invention*

The claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

*The State of the Prior Art*

The state of the art is one of intense interest and development. However, the aspect of employing multiple sequences in an amplification reaction where but one sequence is involved in an amplification reaction or where a primer is allowed to anneal and serve as an active primer in a primer extension reaction subsequent to being treated with an exonuclease is not developed.

*The Relative Skill of Those in the Art*

The relative skill of those in the art that is most closely associated with the claimed invention is high, on par with those that hold a Ph.D. in biochemistry.

*The Breadth of Scope of the Claims*

The claims have sufficient breadth of scope so to encompass amplification of one or a plurality of target sequences in a common reaction where a plurality of primers are present and

wherein said reaction not all primers are permitted to actively prime an extension reaction due to a mismatch on the 3'-terminus.

In order for one of skill in the art to practice the full scope of the claimed invention, the public would have to finely tune the reaction conditions to where a plurality of primers can be used and wherein at least one of the primers will have a mismatch with the target sequence on the 3' terminus. Simultaneously, the mismatch primer must not also effectively anneal to non-target sequences so as to result in the amplification of non-target sequences. Such fine tuning of reaction conditions are imperative to practicing the claimed invention yet the claims have sufficient breadth of scope so to encompass virtually any reaction condition. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385,

> 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

Further attention is directed to the publication of Sommer and Tautz, which shows that effective priming was achieved where but two nucleotides were needed. In view of the limited guidance provided, and the art recognized capacity of effective priming taking place with as little as tow nucleotides on the 3' terminus and wherein the primer extension product will be that of a non-target entity, the need for greater guidance is warranted. Therefore, and in the absence of convincing evidence to the contrary, the specification has not been found to enable the claimed method.

*Response to arguments*

At page 4 of the response received 23 July 2001, hereinafter the response, it is asserted that only routine experimentation would be needed to augment the disclosure and that such efforts do not rise to the level of undue experimentation. Argument is also advanced that the one prophetic example that is provided by the disclosure is more than adequate to enable the full scope of the invention (page 4, bridging to page 5 of the response). Applicant's representative also directs attention to pages 7-10 of the disclosure where prior art documents are cited.

The above arguments have been fully considered and have not been found persuasive towards the withdrawal of the rejection. As set forth above and in the prior Office action, the absence of starting materials and reaction conditions which would enable the full scope of the invention unfairly shifts the burden of enablement from that of applicant to the public.[1] While agreement is seemingly reached in that the specification does provide one example (pages 74-81 of the disclosure) and that there is no *per se* rule that a specification must contain examples of each and every possible permutation encompassed by the claims, such arguments are not found persuasive towards the withdrawal of the rejection in the present case for as set forth in *Fisher*, the level of disclosure varies inversely to the predictability of the art. In the present case the claims are drawn to an area of art, chemical matters, that have been recognized as being unpredictable, *Ibid.* The one example, which is considered to represent but a single species or format of the generic claimed method, is not considered to be an adequate, fully- enabling disclosure. In support of this position, attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.
>
> ***

[1] *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001.

> We are of the opinion that a genus containing such a large number of species cannot properly be identified by the mere recitation or reduction to practice of four or five of them. As was pointed out by the examiner, four species might be held to support a genus, if such genus is disclosed in clear language; but where those species must be relied on not only to illustrate the genus but to define what it is, the situation is otherwise.

Turning to the aspect of pages 7-10 of the disclosure setting forth or identifying prior art articles, it is noted with particularity that a large percentage of same are non-US patent publications. Seemingly applicant is arguing that one of skill in the art would be able to refer to any one or more of these publications in order to overcome any deficiencies in the specification so to enable the claimed invention to the fullest. Applicant's reliance on said publications would cast these documents as disclosing essential subject matter. Enablement cannot be achieved by incorporating by reference non-US patent documents that have not issued as a patent. Even in the case where US patent applications have been identified, currently pending as well as abandoned applications cannot be relied upon for disclosing essential subject matter. If applicant is of the persuasion that these non-US issued patent documents are essential to enabling the claimed invention, then such disclosures should be brought into the subject application. As for said pages 7-10 of the subject disclosure identifying issued US patents, the specification does not identify just which portion of these documents are relative to enabling the subject application and how such prior art disclosures are to be adapted so to achieve the requisite enablement.

At page 6 of the response argument is advanced that the level of skill in the art is perhaps to high as PCR is taught in undergraduate courses. The foregoing argument has been fully considered and has not been found to be persuasive towards the withdrawal of the rejection. It is noted that applicant's remarks are conclusory in nature and are void of any factual underpinning. Specifically, no college catalog has been provided which identifies PCR as being taught in any

undergraduate class. As for PCR being at the skill level of one who holds a Ph.D., it is noted that Kary B. Mullis, Ph.D., and Nobel laureate, is the inventor of PCR and is considered to be representative of the level of skill in the art need to practice the claimed invention.

As for providing evidence to support positions advanced, attention is directed to the prior Office action (and repeated above in the instant Office action) where the publication of Sommer and Tautz was relied upon so to demonstrate just how little complementarity is required in order to achieve functional priming- 2 nucleotides at the 3' terminus. The claimed method, however, does not recite limitations that would take into consideration these art-recognized problematic areas. Given that the Office is charged with reading the claims as broadly as is reasonably possible and the claims have been interpreted as encompassing conditions where non-intended amplification products will result, applicant, not the public, bears the responsibility of fully enabling the claimed method not just where most restrictive conditions are employed but over the full breadth of scope, including those situations where a heterogeneous mixture of nucleic acids are present and conditions are such that target and non-target sequences are present and will be amplified in like fashion. A review of the specification, however, has failed to find a disclosure that enables the full scope encompassed the claims.

3. Claims 53-57 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As presently worded, the kit of claims 53-57 has sufficient breadth of scope so to encompass primers that will hybridize to any and all possible target

sequences, be they known or unknown. The specification has not been found to reasonably suggest that applicant was in possession of any and all possible primer combinations a presently claimed and as such, the specification has not been found to satisfy the written description requirement as set forth in 35 USC 112, first paragraph. In support of this position, attention is directed to the decision of *Vas-Cath Inc. v. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

*Response to argument*

4. At page 8 of the response argument is prefaced by first acknowledging that the Office holds that claims 53-57 are not enabled. It is noted with particularity that the rejection that appears at page 6 of the prior Office action is directed to matters of written description, not enablement. The aspect of enablement was presented in the rejection that spans from pages 2-6 of the prior Office action.

5. Applicant presents argument at page 8 of the response that by limiting the claim to "a kit for amplifying a ***target sequence within a target polynucleotide***" that the skilled artisan must know the nucleotide sequence of the target polynucleotide and "[f]rom this information, primers and the control polynucleotide can readily be prepared using routine laboratory techniques" (emphasis in the original).

6. The above argument has been fully considered and has not been found persuasive for the claims at issue are not drawn to a method of making the claimed oligonucleotide primers and probes, but rather to the product themselves. The specification must provide an adequate written description of the products claimed so to reasonably suggest that applicant was in possession of same. Claims 53-57 are considered to be generic in scope and as such encompass millions of distinct chemical compounds. The limited species disclosed do not provide an adequate written description of the genus; *In re Shokal*. The ease of difficulty required to produce the product is not dispositive of the rejection as it is the specification, not the skill of the artisans, that must provide an adequate written description of the claimed compounds. In support of this position, attention is directed to the decision of *Fiers v. Sugano* 25 USPQ2d 1604-5 (CAFC, January 1993) wherein is stated:

> We also reject *Fiers* argument that the existence of a workable method for preparing a DNA establishes conception of that material. Our statement in *Amgen* that conception may occur, *inter alia*, when one is able to define a chemical by its method of preparation requires that the DNA be claimed by its method of preparation. We recognize that, in addition to being claimable by structure or physical properties, a chemical material can be claimed by means of a process. A product-by-process claim normally is an after-the-fact definition, used after one has obtained a material by a particular process. Before reduction to practice, conception only of a process for making a substance, without a conception of a structural or equivalent definition of that substance, can at most constitute conception of the substance claimed as a process. Conception of a substance claimed *per se* without reference to a process requires conception of its structure, name, formula, or definitive chemical or physical properties. . .
> * * * *
> The difficulty that would arise if we were to hold that a conception occurs when one has only an idea of a compound, defining it by its hoped-for function, is that would-be inventors would file patent applications before they had made their inventions and before they could describe them. That is not consistent with the statute or the policy behind the statute, which is to promote disclosure of inventions.

Attention is also directed to the decision of *University of California v. Eli Lilly and Co.* (CA FC, July 1997) 43 USPQ2d 1398 wherein is stated:

> In claims involving chemical materials, generic formulas usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate written description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what it achieves as a result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of; is not a description of that material.
>
> Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA. See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

At present the claims read on oligonucleotides that are directed to an ever-changing target sequence. Applicant seeks to claim kits that comprise oligonucleotide primers that are directed to sequences not yet discovered. The specification fails to provide an adequate written description of such target sequences or of the oligonucleotide primers that the kit is to comprise.

7. For the above reasons, and in the absence of convincing evidence to the contrary, the rejection is maintained.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 4-6, 11-13, 27-29, 41-43, and 53-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially" in claims 4, 11, 27, 41, and 53 is a relative term that renders the claims indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 5-6, 12-13, 42-43, and 54-57 which depend from said claims 4, 11, and 27, 41, and 53 fail to overcome this issue and are similarly indefinite.

*Response to argument*

At pages 9-10 of the response argument is advanced that the term "substantially" is definite and that the above rejection should be withdrawn. Using claim 4 as an example, applicant directs attention to the last portion of the claim as providing a definition to the term. For convenience the claim, en toto, is reproduced below:

> 4. The method of Claim 2 wherein a modified oligonucleotide primer is included in said combination wherein said modified oligonucleotide primer is substantially identical to said oligonucleotide primer but contains a chemical modification at its 3'-end that prevents degradation, by said 3' to 5' exonuclease, of said 1 to 10 nucleotides. (emphasis added)

While acknowledgement is made of the claim indicating that some modification at the 3' terminus has been effected, it is not clear if this modification is to be applied as the only interpretation of "substantially identical." It is the position of the Office that the phrase "substantially identical" is separate and apart from the description of the characterization at the

3'-terminus of the modified oligonucleotide primer. Support for this two-part interpretation of the claims' language is based in part upon the usage of the term "but." If one were to use of an "identical oligonucleotide primer" as well as a "substantially identical primer" but which has a modified 3' terminus speaks to two different types of primers yet they each contain a modified 3' terminus. Just what constitutes the metes and bounds of "substantially identical" is at issue. Clarification is needed.

***Conclusion***

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L Sisson
Primary Examiner
Art Unit 1655

bls
October 4, 2001